ACUTE TOXICITY SUMMARY

CHLOROPICRIN

(trichloronitromethane; nitrochloroform; nitrochloromethane)

CAS Registry Number: 76-06-2

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**29 μg/m³**
Critical effect(s)	mild respiratory irritation
Hazard Index target(s)	Respiratory System; Eyes

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description		colorless to faint yellow liquid
Molecular formula		CCl_3NO_2
Molecular weight		164.4
Density	1.65 g/cm^3 @ 20°C	
Boiling point		112.4°C
Melting point		-64°C
Vapor pressure		5.7 mm Hg @ 0°C
Flashpoint		not applicable
Explosive limits:		upper = not applicable lower = not applicable
Solubility		0.16 g/100 mL water; miscible in benzene, absolute alcohol, and carbon disulfide
Odor threshold		1.1 ppm (7.3 mg/m³)
Odor description		pungent, sweet, irritating odor resembling flypaper (Prentiss, 1937)
Metabolites		unknown; photodegrades into phosgene
Conversion factor		1 ppm = 6.72 mg/m³ @ 25°C

III. Major uses or sources

Chloropicrin is used as a fumigant for warehouses, cereals and grains. It is also a soil insecticide, and is added in trace amounts as a warning agent in odorless gases such as methyl bromide. Previously, it was used as a chemical warfare agent by the military because of its strong irritancy and potency in inducing lacrimation.

IV. Acute Toxicity to Humans

Data on the effects of chloropicrin on humans were collected post-World War I. The symptomatology in humans following an exposure to 50 mg/m³ for 1 hour includes intolerable irritation to the eyes and upper respiratory tract (Prentiss, 1937). The probable oral lethal dose in humans is between 5 and 50 mg/kg (HSDB, 1994). Inhalation of 2,000 ppm (13,340 mg/m³) for 10 minutes is reported to be lethal (HSDB, 1994). Lethality was also reported following a 10 minute exposure to 2.0 mg/L (2,000 mg/m³) chloropicrin (Prentiss, 1937). Death is due to acute effects on the upper and lower airways. Chloropicrin affects the medium and small bronchi primarily, but also injures the alveoli, resulting in pulmonary edema, which is often the cause of lethality (Clayton and Clayton, 1982; Gonmori *et al*., 1987). Flury and Zernik (1931) reported that exposure to a concentration of 26.8 mg/m³ (4 ppm) chloropicrin for a few seconds renders a person unfit for military action, although no clinical details were provided. Exposure to 1 ppm (6.7 mg/m³) chloropicrin causes immediate lacrimation and eye irritation (Grant, 1986). Systemically, chloropicrin reacts with sulfhydryl groups on hemoglobin to interfere with oxygen transport.

Predisposing Conditions for Chloropicrin Toxicity

Chemical: Persons with preexisting eye, skin, respiratory, or asthmatic conditions might be more sensitive (Reprotext, 1999).

Medical: Individuals with a high level of carboxyhemoglobin (e.g., smokers) may be more susceptible to the effects of chloropicrin on oxygen transport. Persons with underlying cardiopulmonary disease may be more sensitive to the irritant effects on the lung. Persons exposed to other lacrimators or irritants or with prevoius exposure to chloropicrin might be more sensitive (Reprotext, 1999).

V. Acute Toxicity in Laboratory Animals

In guinea pigs and cats the inhalation LC_{Lo} is 800 mg/m³ for 20 min (HSDB, 1994). For rats, the LC_{50} is 96 mg/m³ for 4 hours, and the LC_{50} for mice is 9.9 ppm (66 mg/m³) for 4 hours (HSDB, 1994).

The RD_{50} is the concentration of a chemical in air which is associated with a 50% decrease in respiratory rate. The RD_{50} in animals has a predictable relationship to irritation in man (Kane *et al*., 1979). The RD_{50} in mice for chloropicrin is 53-60 mg/m³ (8-9 ppm) (Kane *et al*., 1979; TeSlaa *et al*., 1986). Chloropicrin exposure at the RD_{50} concentration caused lesions in both the upper and lower respiratory tract in mice (Buckley *et al*., 1984).

Lambert and Jackson (1920) reported on the pathology of chloropicrin poisoning in the dog. Concentrations of 900 to 1000 mg/m^3 for 30 minutes killed more than half the dogs. Extreme lung edema, severe necrosis of the bronchi, congestion of the lung and dilatation of the heart were observed at necropsy. These authors described lethal concentrations in several different species (no sample size reported) to range from 370 (in the cat) to 740 mg/m^3 (in the dog) for 30 minutes.

VI. Reproductive or Developmental Toxicity

No animal studies or human exposures indicate that chloropicrin is embryotoxic or teratogenic.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 4.4 ppb (29 μg/m³)

Study	Kane *et al*., 1979
Study population	mice
Exposure method	inhalation
Critical effects	decrease in respiratory rate by 50% (RD_{50})
LOAEL (RD_{50})	7.98 ppm (54 mg/m³) (RD_{50})
RD_{05}	0.79 ppm (5.3 mg/m³)
Exposure duration	10 minutes
Extrapolated 1 hour concentration	132 ppb (0.89 mg/m³) (0.79ppm * 1/6 h = C * 1 h) (see Table 12 for information on "n")
LOAEL uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Reference Exposure Level	4.4 ppb (0.029 mg/m³; 29 μg/m³)

In mice exposed for 10 minutes to 7.98 ppm chloropicrin, a decrease in respiratory rate by 50% (RD_{50}) was observed. Using the regression equation (y = 9.54 + 44.87 Log x) presented by Kane *et al*. (1979), the concentration associated with a 5% reduction in respiratory rate in mice (RD_{05}) was estimated to be 0.79 ppm. This is similar to the BC_{05}; an interspecies uncertainty factor of 3 and an intraspecies uncertainty factor of 10 were applied to the RD_{05}. The resulting REL is 4.4 ppb.

Level Protective Against Severe Adverse Effects

Eye irritation and lacrimation were observed in humans exposed to chloropicrin at 0.3 ppm (2 mg/m³) or higher for 10 minutes (Prentiss, 1937). AIHA (1993) determined an EPRG-2 of 0.2 ppm (1.3 mg/m³). The intent of the ERPG-2 level is to protect against painful eye irritation and lacrimation. However, the safety factor used to derive this level was not specified. Smyth (1956) stated that exposure to 4 ppm (27 mg/m³) for 2 minutes will "incapacitate a man." Adjusting the concentration for the 2-minute exposure to an equivalent concentration for a 1-hour exposure using the formula $C^n * T = K$, where n = 1, yields a value of 0.13 ppm (0.9 mg/m³). Dividing by a UF of 10 to account for sensitive individuals in the human population results in a level protective against severe adverse effects of 13 ppb (90 μg/m³).

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

Exposure of mice to 336 mg/m³ (50 ppm) chloropicrin for 15 minutes caused death after 10 days (Clayton and Clayton, 1982). Brief exposures to 27 mg/m³ (4 ppm) chloropicrin may cause severe respiratory irritation in addition to vertigo, fatigue, gastrointestinal cramps, and diarrhea in humans (Fairhall, 1949). Application of the standard safety factors (1,000) to the value reported by Clayton and Clayton (1982), and time extrapolation to a 1-hour exposure would yield a concentration for a life threatening level that is lower than the EPRG-3 level of 3.0 ppm (20 mg/m³) recommended by AIHA (1992). NIOSH (1995) lists an IDLH of 2 ppm based on acute inhalation toxicity data in workers and animals. NIOSH also mentions that 4 ppm for a few seconds renders a worker unfit for activity. The IDLH makes no allowance for sensitive individuals.

VIII. References

(AIHA) American Industrial Hygiene Association. Emergency response planning guidelines. Set 1. Akron (OH): AIHA; 1992.

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(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (CD-ROM version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

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